PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 29367	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IL2005/000196	International filing date *(day/month/year)* 16.02.2005	Priority date *(day/month/year)* 16.02.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K31/05 A61P3/10		
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY OF THE...et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 15.12.2005	Date of completion of this report 18.05.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Borst, M Telephone No. +49 89 2399-8648

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2005/000196

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:

   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-21 as originally filed

   Claims, Numbers

   1-5, 8-23 filed with telefax on 15.12.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2005/000196

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1 (part),11 (part),19 (part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1 (part),11 (part),19 (part) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2005/000196

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	19-23
	No:	Claims	1-5,8-18
Inventive step (IS)	Yes:	Claims	19-23
	No:	Claims	1-5,8-18
Industrial applicability (IA)	Yes:	Claims	1-5,8-23
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Clarity (Article 6 PCT)

Present independent claims 1, 11, 19 are not clear, because the term "cannabidiol compound" has not a clearly defined meaning generally accepted in the art.
Therefore, the search and substantive examination are restricted to the compounds according to formula (I).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Documents (D) considered to be relevant to novelty and inventive step

D1: "Cannabis-based medicines--GW pharmaceuticals: high CBD, high THC, medicinal cannabis--GW pharmaceuticals, THC:CBD." DRUGS IN R&D. 2003, vol. 4, no. 5, 2003, pages 306-309, XP009048624 ISSN: 1174-5886

D2: WO 99/53917 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA, REPRESENTED BY THE SEC) 28 October 1999 (1999-10-28)

D3: WO 03/063847 A (GW PHARMA LIMITED; WHITTLE, BRIAN; JAVID, FARIDEH, AFSHIN) 7 August 2003 (2003-08-07)

D4: WEISS LOLA ET AL: "Cytokine production in Linomide-treated nod mice and the potential role of a Th (1)/Th(2) shift on autoimmune and anti-inflammatory processes." CYTOKINE. 21 JUL 2002, vol. 19, no. 2, 21 July 2002 (2002-07-21), pages 85-93, XP002330933 ISSN: 1043-4666

D5: SRIVASTAVA M D ET AL: "DELTA 9 TETRAHYDROCANNABINOL AND CANNABIDIOL ALTER CYTOKINE PRODUCTION BY HUMAN IMMUNE CELLS" IMMUNOPHARMACOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, vol. 40, no. 3, October 1998 (1998-10), pages 179-185, XP000957596 ISSN: 0162-3109

1. Novelty (Article 33(2) PCT)

1.1. The subject-matter of present claims 1-5 is not new in the light of D1.
D1 (page 307, 4th full paragraph) discloses the use of a combined preparation of CBD and THC for the treatment of patients with peripheral neuropathy secondary to diabetes mellitus. THC is known to have psychotropic activity. Thus, by restricting the

independent claim to the amnufacture of a medicament having no psychotropic activity identified novelty appears to be established over D1.

1.2. The subject-matter of present claims 1-5, 8-18 is not new in the light of D2.
D2 (page 3, line 26-30; page 10, line 31-34; page 11, line 12-27; page 23, line 17-19) discloses the use of CBD for its antioxidant property for the treatment of oxidative associated diseases including autoimmune diseases, such as diabetes. Autoimmune diabetes is type 1 diabetes and includes insulitis.
According to D2 (page 6, line 1-6) the cannabinoid has no psychoactive activity.
Moreover, hyperglycemia and/or glucosuria are symptoms common to all diabetes patients. Therefore, the restrictions made to independent claim 1 are not suitable to establish novelty over D2.
The Applicant argues that D2 refers to diabetes as "oxidative associated disease", while the treatment disclosed therein is for diseases caused by oxidative stress.
However, D2 (page 11, line 1-4) defines "oxidative associated disease" as diseases that result at least in part from the prodiction of or exposure to free radicals. Thus "oxidative associated disease" in the sense of D2 are diseases caused by oxidative stress and the Applicant's argument does not apply.
Moreover, it has been submitted that D2 does not provide any evidence for the therapeutic effectiveness of antioxidant cannabinoids in the treatment of diabetes.
Reference has been made to an article according to which antioxidant therapy is not beneficial in diabetes. However, as the application itself provides evidence to the contrary, any argument to the point that the disclosure of D2 was not enabling, fails.

1.3. The subject-matter of present claims 1-5 is not new in the light of D3.
D3 (page 1, line 18-25; page 2, line 28 - page 3, line 21) discloses the use of a cannabinoid composition for the treatment of nausea occurring in diabetes.
Therapeutic use in (i) patients with nausea occurring in diabetes mellitus cannot be distinguished from a therapeutic use in (ii) patients with diabetes, since patient group (i) falls within patient group (ii).
According to D3 (page 4, line 28-35; page 9, line 20-33) CBD is the active principle and a CBD composition substantially free from other cannabinoids or synthetic CBD may be used. Thus, D3 also discloses the use of non psychotropic CBD for the treatment of nausea occurring in diabetes mellitus. Moreover, hyperglycemia and/or

glucosuria are symptoms common to all diabetes patients. Therefore, the restrictions made to independent claim 1 are not suitable to establish novelty over D3.

2. Inventive step (Article 33(3) PCT)

2.1. The subject-matter of present claims 1-5, 7-10 does not involve an inventive step, because the problem of providing an effective treatment is not solved for the whole scope of the claims.

The invention on file is based on the finding that CBD has positive effects in NOD mice. As stated in the application itself (cf. page 17, line 31 - page 18, line 2) NOD mice develop spontaneous autoimmune diabetes and, therefore, represent an experimental model for insulin-dependent diabetes mellitus. Thus, the experimental evidence provided is clearly limited to type 1 diabetes and there are no facts provided supporting an extrapolation to type 2 diabetes. Thus, any subject-matter directed to or including the treatment of type 2 diabetes canot be considered as being solved and, hence, as involving an inventive step.

Hyperglycemia and/or glucosuria are symptoms common to all diabetes patients irrespective of whether type 1 or type 2 diabetes. Thus, the corresponding restriction made to independent claim 1 does not exclude type 2 diabetes. Thus, the scope of claim 1 still includes the treatment of type 2 diabetes, for which the problem of providing an effective therapy is not solved.

2.2. Being not new the subject-matter of claims 1-5, 8-18 does not involve an inventive step.

2.3. Once novelty is established the invention appears to involve an inventive step in the light of D4 and D5.

Like the application on file D4 deals with the treatment of autoimmune diabetes and insulitis in NOD mice. According to D4 (figure 1; figure 4; page 87-91, paragraph entitled "Discussion") linomide prevents autoimmune insulitis and diabetes mellitus in NOD mice by lowering levels of TNFα, IL-1ß, IFNy and IL-12, while increasing levels of IL-4, IL-6 and IL-10. D4 concludes that "Linomide and/or non-immunosuppressive agents with a similar mode of action may prove to be promising tools for the treatment of type I diabetes mellitus". D4 does not disclose a CBD compound.

The objective technical problem to be solved in the light of D4 was to provide further agents with a mode of action similar to linomide and effective in the treatment of type I diabetes mellitus.

D5 (page 183-184, paragraph entitled "Discussion") discloses for CBD a reduction in TNFα, IFNy, IL-1 and in IL-10. The effect of CBD on IL-10 is contrary to that of linomide. As the focus of D4 is on the level of IL-10 and the effects thereupon are opposite for linomide and CBD, the Applicant's argument to the point that D5 rather teaches away from the subject-matter of claim 1 appears correct.